

# Creating Special Variance Structures for Coxme

Terry Therneau  
Mayo Clinic

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## 1 Introduction

The `coxme` function allows the user to create their own variance handling routines. This allows the program to be extended in ways not visualized by the author. This short vignette gives an example of such a structure.

We would like to fit the following random effects model

$$\lambda(t) = \lambda_0(t)e^{X\beta + Zb} \quad (1)$$

$$b = N(0, \sigma^2 R) \quad (2)$$

$$R_{ij} = \begin{cases} 1 & \text{if } i = j \\ \rho & \text{otherwise} \end{cases} \quad (3)$$

The motivating example is the use of gene sets in a lung cancer study. Here  $X$  is a matrix of known covariates such as grade and stage of the tumor and  $Z$  is a matrix of gene expression levels from a microarray experiment; each column of  $Z$  is one gene from a specified gene set. There is a separate  $Z$  for each gene set, the number of columns of  $Z$  typically ranges from 10 to 100.

When  $\rho = 1$  this model constrains all of the coefficients to be identical. This is equivalent to a shrinkage method found commonly in the the utilization of questionnaires, where all of the questions in a particular domain are summed to get an overall score for that domain which is then used as a covariate in a model.

The `coxme` code for this model will be

```
> fit <- coxme(Surv(time, status) ~ stage + histology + (z|1),  
              data=mydata, varlist=gexchange)
```

## 2 Variance functions

The variance function `gexchange` consists of a list with 3 elements: an initialize function, a generation function, and a closing function.

```
> gexchange <- function() {  
  out <- list(initialize = geinit,
```

```

        generate = gegenerate,
        wrapup   = gewrapup)
class(out) <- "coxmevar"
out
}

```

## 2.1 Initialization function

The initialization function is often the most tedious to create. It is responsible for 4 tasks:

1. Verify that the input data is consistent with the variance function
2. Process any initial values given by the user
3. Transform parameters
4. Create the return value containing the starting estimates and the control parameters.

Input arguments are

- `vinit`: a list or vector of initial estimates for the parameters, as supplied by the user. This may be empty. An example would be `vinit=list(sigma=c(.1, .3), rho=c(.1, .8))`. This would evaluate the fit over a 2 by 2 grid of values, the best fit found becomes the starting estimate for the full maximization. The routine below requires that the starting estimates be named and that both are supplied, other routines could be more or less flexible.
- `fixed`: a vector of fixed values for the parameters, as supplied by the user. For instance adding the clause `variance=list(rho=.4)` could be used to fit a model where  $\rho$  is fixed at 0.4.
- `intercept`: Does the term include an intercept. This would be true for a term like `(1+ trt | site)`, but is invalid for this variance function.
- `G`: A vector or matrix containing the grouping variables found on the right hand side of the vertical bar.
- `X`: A matrix of covariates found on the left of the vertical bar.
- `sparse`: User specified parameter which advises with respect to the use of sparse matrices. It is ignored in this function.

```

> geinit <- function(vinit, fixed, intercept, G, X, sparse) {
  if (length(G) >0)
    stop("This function does not handle groupings")
  if (length(X)==0)
    stop("No covariates given!")
  if (ncol(X) <2)
    stop("Only one random slope, correlation is irrelevant")

  if (length(vinit) >0) {

```

```

    if (length(vinit) !=2) stop("Wrong length for vinit")
    indx <- match(names(vinit), c("sigma", "rho"))
    if (any(is.na(indx)))
      stop("Unrecognized parameter name in vinit values")

    theta <- list(vinit[[indx[1]]], vinit[[indx[2]]])
  }
else theta <- list(c(.05, .2, .6)^2, c(.01, .5, .9))

which.fixed <- c(FALSE, FALSE)
if (length(fixed) >0) {
  indx <- match(names(fixed), c("sigma", "rho"))
  if (any(is.na(indx)))
    stop("Unrecognized parameter name in vfixed values")
  if (is.list(fixed)) {
    if (any(sapply(fixed, length) !=1))
      stop("Any fixed parameter must have a single value")
    fixed <- unlist(fixed)
  }
  which.fixed[indx] <- TRUE
  theta[which.fixed] <- fixed[which.fixed]
}

if (any(theta[[1]] <=0)) stop("Variance must be >0")
if (any(theta[[2]] <0) || any(theta[[2]] >=1))
  stop("Correlation must be between 0 and 1")

theta[[2]] <- theta[[2]]/(1-theta[[2]])

# In the shape of X, first column=1, second =2, etc
xmap <- matrix(rep(1:ncol(X), each=nrow(X)), nrow(X))

list(theta=lapply(theta, log)[!which.fixed], imap=NULL,
      X=X, xmap=xmap,
      parms=list(theta=sapply(theta, function(x) x[1]),
                  fixed=which.fixed,
                  xname=dimnames(X)[[2]], nvar=ncol(X)))
}

```

The first six lines check that this variance structure is relevant for the random term as specified. The next block of statements reads in any initial values for the parameters. The parameter vector as a whole is  $\theta = (\sigma^2, \rho)$ . If no initial values were given then a default grid of values for the initial search is  $\sigma = .05, .2, .6$  and  $\rho = .01, .5, .9$ . Note that the final  $\theta$  is always a list, even if all the elements parameters only have length 1

The next block of lines checks for any fixed parameters. If any are found the corresponding elements of `which.fixed` are set and the initial value is reset. For iteration we will use

transformed parameters:

$$\begin{aligned}\tilde{\theta}_1 &= \log(\sigma) \\ \tilde{\theta}_2 &= \log\left(\frac{\rho}{1 - rho}\right)\end{aligned}$$

The actual optimization is done by the `optim` routine, and need it to operate in an unconstrained space. No transform is required for the fixed parameters, which are never made visible to the `optim` routine.

Finally we create the returned value, which is a list with components:

- `theta`: A list with one element for each parameter value which is to be optimized, each element is a vector of potential starting values, on the transformed scale. The list can be NULL, for instance when all the parameters are fixed.
- `imap`: mapping between intercept terms and coefficients
- `X`: the covariate matrix, possibly transformed, an example might be prescaling
- `xmap`: mapping between slopes and coefficients
- `parms`: an arbitrary list which will be passed forward to the generate and wrapup routines, the main `coxme` code does not examine it.

The `imap` and `xmap` vectors are important for some calculations but not here. For instance, in familial studies the per-subject random intercepts are correlated within familial blocks. For storage and computational efficiency the relevant variance function uses a `bsdmatrix` object for the variance. This requires that all the coefficients for a family are adjacent in the parameter vector, but the subject identifier variable might not be in this order. A value for `imap` of 1, 7, 4, ... would map subject 1 to coefficient 1, subject 7 to coefficient 2, subject 3 to coefficient 4, etc. A valid `imap` value will be a matrix with one column per grouping variable (the term (1|teacher/school) would have 2 columns), each row contains the coefficient number for that subject. The `xmap` matrix is the same shape as `Z`, and shows for each subject the coefficient number which multiplies the relevant covariate.

## 2.2 Generation function

The input arguments to this function are the current vector of iterated parameters, along with the list of parameters supplied by the `init` function. The result of the routine is the covariance matrix  $\Sigma$  of the random effects for the term.

One of the greatest challenges for this routine is to guarantee that the resulting matrix is positive definite to a sufficient degree that the creation of  $\Sigma^{-1}$  will give a full rank result. The Affymetric gene-set for which this routine was developed had values between 6 and 15, which in turn means that any coefficient less than about .0001 has an effect size of effectively zero. Very small variances, which lead to  $b$  vectors of that size, need not be pursued to a bitter end of  $\log(\epsilon) \rightarrow -\infty$  for  $\epsilon \rightarrow 0$ . For many gene sets  $\sigma = 0$  is the actual MLE, but the change in LL for these smallest values becomes so tiny as to approach machine precision. The second limit in the routine came from a particular data set where an intermediate guess in the maximization gave

too large a variance, far beyond what is biologically feasible, which in turn led to overflow of the exp function in calculation of  $\exp(X\beta + Zb)$ .

```
> gegenerate <- function(newtheta, parms) {
  safe.exp <- function(x, emax=20) {
    exp(pmax(-emax, pmin(emax, x)))
  }

  theta <- parms$theta
  if (!all(parms$fixed))
    theta[!parms$fixed] <- safe.exp(newtheta)

  correlation <- theta[2]/(1+theta[2])
  variance <- min(theta[1],20) #keep it out of trouble
  varmat <- matrix(variance*correlation, nrow=parms$nvar,
                    ncol=parms$nvar)
  diag(varmat) <- variance
  varmat
}
```

## 2.3 Wrapping up

The wrapup routine has two tasks. The first is simple: to return any transformed parameters back to their original scale. The second is to add names and structure to the results so that they will print with reasonable names.

The return value is the vector of final  $\theta$  values, and a list containing the random coefficient vector  $b$ .

```
> gewrapup <- function(newtheta, b, parms) {
  theta <- parms$theta
  theta[!parms$fixed] <- exp(newtheta)
  correlation <- theta[2]/(1+theta[2])

  rtheta <- list('(Shrinkage)' = c(variance=theta[1],
                                  correlation=correlation))

  names(b) <- parms$xname
  list(theta=rtheta, b=list(X=list(b)))
}
```

Here then is an example using gexchange and a null gene set which has no relevance. The coxme routine accepts either a coxmevar object or a function which generates such an object as the argument to the varlist option.

```
> gexchange <- function() {
  out <- list(initialize = geinit,
              generate = gegenerate,
              wrapup = gewrapup)
```

```

      class(out) <- "coxmevar"
      out
    }
  }
  > require(coxme)
  > set.seed(1960)
  > n <- nrow(lung)
  > dgene <- matrix(rnorm(n*12, mean=8, sd=2), ncol=12)
  > fit <- coxme(Surv(time, status) ~ age + ph.ecog + (dgene | 1),
    data=lung, varlist=gexchange)
  > print(fit)

Cox mixed-effects model fit by maximum likelihood
Data: lung
events, n = 164, 227 (1 observation deleted due to missingness)
Iterations= 12 51

      NULL Integrated      Fitted
Log-likelihood -744.4805 -734.9533 -734.9522

      Chisq df      p      AIC      BIC
Integrated loglik 19.05  4 7.6688e-04 11.05 -1.35
Penalized loglik 19.06  2 7.2962e-05 15.05  8.85

Model: Surv(time, status) ~ age + ph.ecog + (dgene | 1)
Fixed coefficients
      coef exp(coef)  se(coef)      z      p
age      0.01128166  1.011346 0.00931941 1.21 0.23000
ph.ecog  0.44348947  1.558135 0.11583153 3.83 0.00013

Random effects
Group      Variable      Std Dev      Variance
(Shrinkage) variance  5.191577e-04 2.695247e-07
correlation 9.511232e-01 9.046354e-01

> coxme(Surv(time, status) ~ age + ph.ecog + (dgene | 1),
  data=lung, varlist=gexchange,
  vfixed=c(sigma=.01))

Cox mixed-effects model fit by maximum likelihood
Data: lung
events, n = 164, 227 (1 observation deleted due to missingness)
Iterations= 11 47

      NULL Integrated      Fitted
Log-likelihood -744.4805 -737.0109 -734.7571

      Chisq df      p      AIC      BIC
Integrated loglik 14.94 3.00 0.00186950  8.94 -0.36
Penalized loglik 19.45 3.11 0.00025196 13.22  3.57

```

```
Model: Surv(time, status) ~ age + ph.ecog + (dgene | 1)
```

```
Fixed coefficients
```

	coef	exp(coef)	se(coef)	z	p
age	0.01151817	1.011585	0.009334737	1.23	0.22000
ph.ecog	0.44600678	1.562062	0.116043415	3.84	0.00012

```
Random effects
```

Group	Variable	Std Dev	Variance
(Shrinkage)	variance	0.1000000	0.0100000
	correlation	0.9990895	0.9981798

### 3 Alternate arguments

Arguments to a variance function do not need to be passed via the `vinit` and `vfixed` arguments of `coxme`. Here is a very simple variance function which was used when testing out a model with random treatment effects, i.e.

```
> coxme(Surv(time, status) ~ stage + trt + (1+trt | site), data=mydata,
        varlist=myvar(c(.1, .2, .4)))
```

The model has a random intercept and slope for each site, and during testing we wanted to evaluate this for various fixed values of the three parameters: variance of the random intercepts, variance of the random slopes, and correlation.

```
> myvar <- function(var) {
  initialize <- function(vinit, fixed, intercept, G, X, sparse) {
    imap <- as.matrix(as.numeric(G[[1]]))
    ngroup <- max(imap)
    v2 <- var
    v2[3] <- v2[3]*sqrt(v2[1]*v2[2]) #covariance
    list(theta=NULL, imap=imap, X=X, xmap=imap+ngroup,
          parms=list(v2=v2, theta=var, ngroup=ngroup))
  }
  generate <- function(newtheta, parms) {
    theta <- parms$v2
    varmat <- diag(rep(theta[1:2], each=parms$ngroup))
    for (i in 1:4) varmat[i,i+ngroup] <- varmat[i+ngroup,i] <- theta[3]
    varmat
  }

  wrapup <- function(newtheta, b, parms) {
    theta <- parms$theta
    rtheta <- list(site=c(var1=theta[1], var2=theta[2], cor=theta[3]))
    b <- matrix(b, ncol=2)
    dimnames(b) <- list(NULL, c("Intercept", "Slope"))
  }
}
```

```

      list(theta=rtheta, b=list(site=b))
    }
    out <- list(initialize=initialize, generate=generate, wrapup=wrapup)
    class(out) <- 'coxmevar'
    out
  }
}

```

This routine ingores any vinit or vfixed arguments and does absolutely no error checking; it assumes for instance that  $Z$  has exactly one column and that there is exactly one grouping variable; the input argument is assumed to be length three with valid values. The routine's advantage was that it took only a few minutes to write. (I don't generally recommend using no error checks, by the way.) The random effects  $b$  are arranged as the four intercepts followed by the four slopes, we display them as a matrix for the user's convenience.